BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Office Action has rejected Claims 7-18 under 35 U.S.C. §112, first paragraph, for allegedly being non-enabling. Finally, Claim 18 has been rejected under 35 U.S.C. §101, for allegedly failing to set forth the steps of the process recited therein.

Applicants have amended the claims, which, where considered with the comments herein, are deemed to place the present case in condition for allowance. Favorable action is respectfully requested.

Applicants have amended claims 1, 7, 14, 20 and 21. More specifically, applicants have amended Claim 1 by correcting the obvious error in the structure depicted therein. In addition, applicants have deleted the phrase "preferably n is 1" and have recited this subject matter in newly added Claim 24. Further applicants have amended Claim 1 to recite that it is directed to the compound of formula I and solvates thereof, prodrugs thereof, tautomers thereof, and isomers thereof. Since the term "pharmaceutically acceptable derivatives" included these elements, its recitation was redundant to some extent; in order to correct the grammatical error the term "pharmaceutically acceptable derivatives" thereof was deleted from Claim 1.

Claims 7, 12, 14 and 20-21 were amended to replace the term "including" with comprising. Such an amendment does not narrow the scope thereof.

Claims 18 and 22 have been deleted without prejudice. Applicants have not, however, abandoned the subject matter therein, but reserve the right to file a continuation application directed thereto. Moreover, the cancellation of Claim 18 renders the rejections thereof under 35 U.S.C. §§112, and 101 moot. Withdrawal thereof is respectfully requested.

A marked up version showing the changes made to the claims in appended hereto. It is entitled "Version With Marking to Show Changes Made".

No new matter has been added to the application.

Applicants respectfully submit that the Amendment to the claims overcome the rejections thereof under 35 U.S.C. §112, second paragraph. Withdrawal thereof is respectfully requested.

Pursuant to the rejection of Claims 7-18 under 35 U.S.C. §112, first paragraph, the Office Action admitted that the specification is enabling for treating ischemic diseases. However, it alleges that the application is not enabling for the prophylactic and/or treatment of disorders related to the neuronal damage of the central nervous system. It alleges that it does not believe that the compounds of the present invention are useful for the prophylaxis and treatment of disorders related to the neuronal damage of the central nervous system.

Applicants agree that the application is enabling for treating ischemic diseases. However applicants respectfully submit that the application is enabling for the prophylaxis and treatment of disorders related to the neuronal damage of the central nervous system.

Applicants respectfully submit that the Office Action has not made out a prima facie case of non-enablement. Case law has held that the United States Patent and Trademark Office has the burden to establish a reasonable basis to question the enablement provided by the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); MPEP §2164.04.

Case law has held that a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enablement requirement under 35 U.S.C. §112, unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the Marzocchi court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Id., 439 F.2d at 224, 169 USPQ at 370.

The United States Patent and Trademark Office has not provided any evidence that contradicts the statements in the application that the compounds of the present invention have the requisite utility. The Office Action has cited no reference which corroborates its position. Although it has cited one reference, that reference as explained herein below does not support the position of the U.S. Patent and Trademark Office. It has improperly placed the burden upon applicants to support its allegations which is contrary to case law.

The Office Action cites Vajda. But Vadja does not support the position of the Office Action.

On any balanced reading Vajda supports the view that common pathways

are important in a wide variety of neurological diseases, that glutamate triggers excitotoxicity and NMDA receptors are involved. It is true that Vajda also suggests that known drugs may offer some potential in neurological diseases and that the use of known drugs may save on the need to develop new drugs. However, this latter point is of little relevance with respect to the present invention. Moreover, Vajda does not state, as the Office Action has alleged, that compounds which are NMDA antagonists and sodium channel blockers are not useful for the treatment or prophylaxis of neurological disorders.

Further applicants enclose various publications which support the role of NMDA antagonists and voltage-sensitive sodium channel blockers in a broad range of neurological indications. Furthermore, these publications employ assays to define the NMDA blocking and sodium channel blocking activities of the compounds described that are substantially similar to the NMDA blocking and sodium channel blocking assays used to define the activities of the compounds of the present invention. A brief description of the patents is provided below:

1. U.S. Patent No. 6,376,530 to Claiborne, et al. This patent describes and claims a series of NMDA receptor antagonists and the therapeutic use of such compounds. In fact, the background in Column 1 and 2 provides a useful overview of the potential therapeutic indications for NMDA antagonists.

2. U.S. Patent No. 6,063,774 to Nikam. This patent also describes a group of NMDA receptor antagonists and methods of treatment using such compounds. A ligand binding assay was used to determine the NMDA receptor binding properties of the compounds.

Claim 8 thereof is directed to a method for the treatment of neurodegenerative disorders and then lists numerous disorders which overlap substantially with those of the present invention.

3. U.S. Patent No. 6,245,777 to Grauert, et al. This patent describes and claims a group of compounds which are blockers of the voltage dependent sodium channel and the therapeutic use of such compounds.

Column 2 lines 42-51 lists various diseases and conditions which may be treated with sodium channel antagonists. Claims 15-20 thereof are drawn to methods of treating disorders caused by overstimulation of voltage-dependent sodium channel using the sodium channel antagonists described therein.

Column 2 lines 52-55 describes a ligand binding assay for determining antagonism of the test compounds at voltage-sensitive sodium channels using labeled batrachotoxin (BTX). Column 2 lines 63-67 describe an assay to determine the blocking of veratridine-induced activity; veratridine is a toxin which opens the sodium channel.

4. U.S. Patent Nos. 6,355,652 and 6, 387,921 to Grauert et al. These related patents are similar to 6,245,777 discussed above, except that the claims also include Alzheimer's disease as a further disease which may reasonably be expected to be treated with a voltage dependent sodium channel antagonist.

Again assays involving BTX displacement and blockage of veratridine-induced activity were used to demonstrate the sodium channel blocking properties of the compounds.

The above noted U.S. patents provide a useful overview of the state of the art in respect of the role of NMDA receptor antagonists and voltage sensitive sodium

channel antagonists in treating various neurological diseases and conditions. They also provide an indication of assay systems which may be used to determine NMDA receptor activity and activity at voltage sensitive sodium channels. Some of the assays used to define the activity of the compounds of the present invention are substantially similar to the assay used in the cited patents. For example, the NMDA receptor activity of the compounds of the present application is assessed in a ligand binding assay using [^{3}H]-ifenprodil, the exact ligand used in U.S. Patent No. 6,376,530. Antagonism at voltage sensitive sodium channels was assessed in the present invention in both a labeled batrachotoxin binding assay and an assay to block veratridine-induced activation of sodium channels. These very same types of assays are used in U.S. Patent No. 6,245,777, U.S. Patent No. 6,355,652 and U.S. Patent No. 6,387,921 to assay activity.

In summary, it is clear that both the NMDA receptor and voltage sensitive sodium channels are well established targets for intervention in neurological conditions and diseases. In view of the common pathways implicated in many of these diseases and conditions, antagonists of either of these targets are considered by those skilled in the art to be useful across a broad therapeutic spectrum. When compared with the state of the art it is clear that the assays used in the present application are accepted as being reasonably predictive of activity against these targets.

Further with respect to the comments of the Office Action on page 5 lines 3-7 that there no known drugs which successfully reverse the course of disease, such as Alzheimer's diseases, Parkinson's disease ALS, it is submitted that treatment does not require the reversal of the course of a disease or the cure of that disease. There are of course treatments available for these diseases today including Alzheimer's disease; for

example Aricept, Exelon and Reminyl are all approved therapeutics. Moreover, it is noted that the cited patents include methods of treatment claims to a broad range of disorders including diseases such as Alzheimer's disease, Parkinson's disease, ALS, and the like. Thus, it is apparent that there is precedent for the United States Patent and Trademark Office to permit the claims to recite the use of compounds for the treatment and/or prophylaxis of these diseases.

Thus, in view of the enclosed evidence the utility recited in claim 7, et seq. is credible. Therefore the application is enabling for the subject matter recited therein. Thus the rejection of Claims 7-18 under 35 U.S.C. §112, first paragraph is overcome. Withdrawal thereof is respectfully requested.

Whereby the parent case is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Mark J. Cohen
Registration No. 32,211

Scully, Scott, Murphy & Presser
400 Garden City Plaza
Garden City, New York 11530
(516) 742-4343

MJC:lf

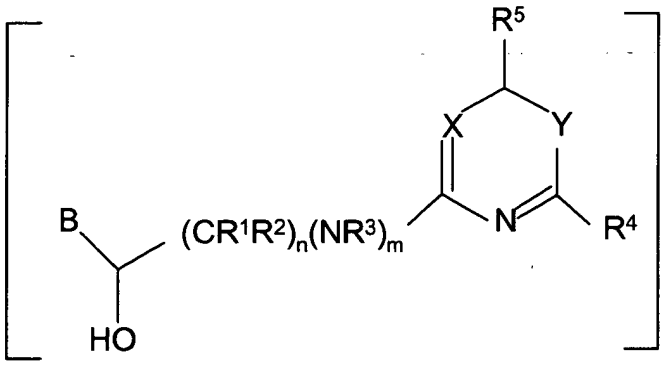
"VERSION WITH MARKINGS TO SHOW CHANGES"

IN THE CLAIMS:

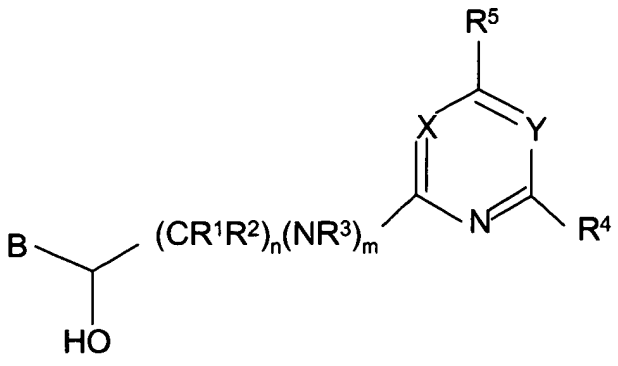
Please cancel Claims 18 and 22 without prejudice:

Please amend Claims 1, 7, 14, 20 and 21 as follows:

1. (Twice Amended) A compound[s] of formula (1)



(1)



wherein

B is optionally substituted aryl;

R^1 and R^2 are the same or different and are independently [selected from] hydrogen or C_{1-3} alkyl;

n is 1 or 2[, preferably n is 1];

m is 0 or 1;

R^3 is hydrogen or acyl;

R^4 and R^5 are the same or different and are independently selected from amino, alkylamino, dialkylamino, arylamino and C_{2-8} cycloalkylamino;

one of X and Y is CH and the other is N and salts thereof, solvates thereof, [pharmaceutically acceptable derivatives thereof,] prodrugs thereof, tautomers thereof [and/or] or isomers thereof.

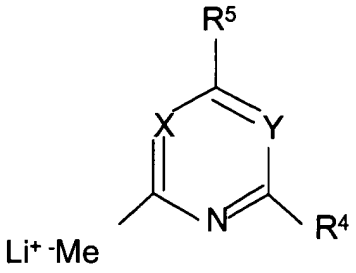
7. (Amended) A method for the prophylatic or therapeutic treatment of one or more disorders related to neuronal damage of the central nervous system [including the step of] comprising administering to a subject in need thereof an effective amount of a compound of formula (1) as claimed in Claim 1.

12. (Amended) A method for the prophylactic or therapeutic treatment of one or more disorders related to neuronal damage of the peripheral nervous system [including the step of] comprising administering to a subject in need thereof an effective amount of a compound of formula (1) as claimed in Claim 1.

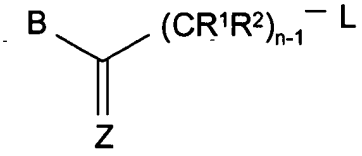
14. (Amended) A method for the prophylactic or therapeutic treatment of one or more conditions related to N-methyl-D-aspartate (NMDA) receptors [including the step of] comprising administering to a subject in need thereof an effective amount of a compound of formula (1) as claimed in Claim 1.

20. (Amended) A process for the preparation of a compound of formula (1) as claimed in claim 1 where m is 0 [including the step of] comprising:

reacting a compound of the formula



[where X, Y, R^4 and R^5 are as defined in Claim 1] with a compound of the formula (2)



(2)

[where R^1, R^2, B and n are as defined in Claim 1.]

wherein

B is optionally substituted aryl;

R^1 and R^2 are the same or different and are independently hydrogen or C_{1-3} alkyl;

n is 1 or 2;

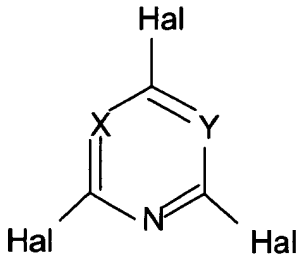
R^4 and R^5 are the same or different and are independently selected from amino, alkylamino, dialkylamino, arylamino and C_{2-8} cycloalkylamino;

X and Y are independently selected from CH, or N provided at least one of X and Y is N;

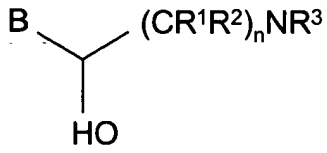
L is a leaving group and Z is a group capable of being converted to hydroxyl.

21. (Amended) A process for the preparation of a compound of formula (1) as claimed in claim 1 wherein m is 1 [including the steps of] comprising:

(i) reacting a compound of formula



[where X and Y are as defined in claim 1 and Hal is a halogen or halogen-like substituent] with a compound of formula (3)



(3)

[where B, R^1, R^2, R^3 and n are as defined in claim 1]; and

(ii) reacting product of step (i) with appropriate amine(s) to afford a compound of formula (1) by substitution of Hal[.] ,

B is optionally substituted aryl;

R^1 and R^2 are the same or different and are independently hydrogen or C_{1-3} alkyl;

n is 1 or 2;

Hal is a halogen or halogen like substituent; and

X and Y are independently selected from CH, or N provided at least one of X and Y is N.